PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

TREANNIE, Lisa, M.
Ropes & Gray LLP
One International Place
Boston, MA 02110-2624
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 02 February 2006 (02.02.2006)	
Applicant's or agent's file reference GUH-PWO-007	IMPORTANT NOTICE

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/023014	16 July 2004 (16.07.2004)	18 July 2003 (18.07.2003)

Applicant
GEORGETOWN UNIVERSITY et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.+41 22 740 14 35	Authorized officer Athina Nickitas-Etienne Facsimile No.+41 22 338 89 95

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference GUH-PWO-007	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/023014	International filing date *(day/month/year)* 16 July 2004 (16.07.2004)	Priority date *(day/month/year)* 18 July 2003 (18.07.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GEORGETOWN UNIVERSITY		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 23 January 2006 (23.01.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Athina Nickitas-Etienne Telephone No. +41 22 338 89 95

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/023014	16.07.2004	18.07.2003

International Patent Classification (IPC) or both national classification and IPC
G01N33/574, G01N33/569, C12Q1/68, G01N33/573, C07K14/47, C07K14/79, C07K14/82, A61K48/00,

Applicant
GEORGETOWN UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hoesel, H Telephone No. +49 89 2399-8693

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/023014

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/023014

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 46-52

because:

☒ the said international application, or the said claims Nos. 46-52 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,3-10,12-17,19-24,60,62-72 (in part); 2,11,18,61

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24,50,60-62
	No:	Claims	46-49,51,52
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24,46-52,60-72
Industrial applicability (IA)	Yes:	Claims	1-24,60-72
	No:	Claims	

2. Citations and explanations

   see separate sheet

The following documents have been taken into account during examination:

D1: WO-A-99/29890
D2: WO-A-02/08764
D3: Anderson. S. et al, Am- J. Pathol. vol. 151/1, 1997, p. 25 - 31
D4: WO-A-02/78695
D5: Noriyuki Y. et al, Cancer Gene Therap. vol. 9, 2002, p. 624 - 630
D6: DATABASE WPI Section Ch, Week 200260 Derwent Publications Ltd., London, GB; Class B04, AN 2002-563528 XP002305239 & KR 2002 012 838 A (BIOGRAND CO LTD) 20 February 2002 (2002-02-20)
D7: Veldman T. et al, PNAS, vol. 100, 08.07.03, p. 8211-8216
D8: Berger A. et al, Am. J. Pathol., vol. 161/2, 2002, p. 603-610

SECTION III:

1. Claims 46-52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

SECTION IV:

2. The common inventive concept linking together the various alternatives listed in claim, is the provision of a method for the diagnosis of cervical cancer based on the detection of at least two biomarkers. This generic concept as well as the selection of primary biomarker is neither new nor inventive in view of the state of the art: D1 for instance discloses diagnostic assays based on the detection of one or more nucleic acids selected from HPV E6 (participating in E6-Myc interaction, cf. claims 1, 3, 6); D2, pertains to the detection of papilloma virus associated biomarkers (E4, E6 or E7) with cell proliferation markers, e.g. CDC6, MCM2, MCM3, MCM4, etc. (cf. D2 claims 1 - 4, 6, 10, 12, 13, 18); D3 discloses that telomerase may serve as diagnostic marker for cervical neoplasia, independent of the known HPV marker E6, und thus renders obvious the combination of E6 (participating in E6-Myc interaction) and telomerase (D3, abstract. p. 27/28, Results). D6 discloses diagnostic kits designed

for the combined detection of HPV16/18 E6 (cf. item 3.1 below) and E7 proteins and MCM5,

Independent claims 25/30, 31/37, 38/45, 46/52 and 53/59 not recite the concept of combination. Thus, neither the combination concept nor the selection of the primary biomarker can provide a common inventive concept within the meaning of Rule 13.2 PCT linking together the various combinations covered by claim 1. Treatment of cervical cancer by means of targeting one biomarker associated with the malignancy is already known. D4 and D5, for instance, disclose treatment of cervical neoplasia by means of inhibition of telomerase activity by administration of specific c-myc/telomerase inhibitors (D4, abstract, claims 54, 55, p. 30, lines 13 - 1) or antisense nucleic acids (D5, abstract and the paragraph extending between pages 629 and 3630).

No other common or corresponding technical features could be identified that establish a common concept linking together the various diagnostic combinations or the various inventive therapeutical approaches. Consequently, the application is considered to contain seven separate groups of inventions based on the choice of the primary diagnostic marker/therapeutical target as identified in the international search report.

The applicant chose not to pay additional search fees. Consequently, the search has been limited to the first invention identified in the claims, i.e. diagnostic combinations comprising telomerase/hTERT as primary diagnostic and therapeutical biomarker.

SECTION V:

3. Treatment of cervical cancer by way of targeting and inhibiting telomerase expression or activity is already known. D4 describes therapeutical inhibition of telomerase activity by core-modified porphyrin derivatives, D5 pertains to an antisense approach to inhibit hTERT expression.
Thus D4, anticipates the subject-matter of claims 46, 51 and 52, D5, anticipates the subject- matter of claims 46-49, 51 and 52 (Art. 33(2) PCT). The subject-matter of claim 50 is considered to be a priori obvious in view of D4 or D5 (Art. 33(3) PCT).

A particular technical teaching going beyond common and per se trivial assumptions is missing. Thus, the subject-matter of claims 46 - 52 additionally lacks substantial support contrary to Art 6 PCT.

4. Diagnostic methods comprising detection of hTERT and at least one of the further biomarkers listed in claim 1.

4.1. What does myc-E6 interaction mean?
Having regard to D7, no HPV E6 dependent molecular alterations of c-myc have yet been identified. The application does not provide a supported disclosure going beyond this state of the art. Thus, it seems that E6 activates hTERT promoter and increases hTERT expression by coassociation with c-myc. Thus, in the absence of identifiable structural changes of Myc, the relevant marker to be assay for in Myc-E6 interaction is HPV E6 itself.

4.2. According to D3, telomerase is a marker for cervical cancer independent of HPV E6/E7. HPV E6 (as part of the E6-myc interaction) and E7 have been used alone or in combination with other biomarkers in the diagnosis of cervical cancer (cf. D1; D6, both disclosing methods based on analysis of the status of HPV E6 and E7) in view of the disclosure of D3 a skilled person would regard the combination of hTERT as diagnostic biomarker with the known biomarkers E6 and or D7 as obvious, particularly as an increase of sensitivity could be expected.

Thus, the method according to claims 1, 2, 6, 7, 9 - 11, 15, 17, 18, 22, 23, 60, 61, 65, 66 and the kit according to claims 69 - 72 is considered to lack an inventive step in view of D3 alone when taken in combination with D1 or D6.

4.3. Insulin-like growth factor binding protein 3 (IGFBP-3), transferrin receptor, beta catenin, c-myc and telomer length appear to have been known before the effective date of this application as markers for cervical cancer as set out in the description or D8 being involved in the development of cervical cancer.

In this instance the inclusion as diagnostic biomarker appears to be primarily obvious. Particular advantages or significance associated with the choice of one or more of

these markers has not been demonstrated.

Consequently, claims 3 - 5, 8, 12 - 14, 16, 19 - 21, 24,62 - 64, 67 and 68 seems to lack an inventive step, contrary to Art. 33(3) PCT.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.